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Reminiscence

Remembering Yellapragada SubbaRow

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The treatment of psoriasis vulgaris in the first half of the 20th century revolved on the intake of arsenical preparations and undecylenic acid[1] and the topical use of mainly keratolytics, chrysarobin, tar regimens, and dithranol formulations. In 1951 a major event leading to a dramatic change occurred when a 36-year-old man known only by the initials L.R. had a remission at New York's Kings County Hospital with aminopterin conceived and developed by Yellapragada SubbaRow as an anti-cancer drug.[2–4] Because of ambivalent reports about aminopterin's toxicity, this might have found a footnote in medical history but for the switch from aminopterin to its relatively less toxic analog methotrexate made by Edmundson and Guy of Pittsburgh.[5]

Most dermatologists are, however, unaware of this significant role by India-born SubbaRow (Su as in supine and Row as in tao) in the introduction of methotrexate, also developed in his laboratory, for the treatment of psoriasis. SubbaRow was born in Andhra Pradesh, India, on January 12, 1895.[6] He sought in religion an escape from family poverty but was directed by the Ramakrishna Mission, a religious order, to modern medicine. His close brush with death from sprue while studying at Madras Medical College exposed the inadequacies of early 20th century Western medicine. His miraculous recovery with the help of herbal juices, the main ingredient being *Eclipta alba* (which much later was found to be a rich source of folic acid), and his consequent fascination with the ayurvedic theory of pathogenesis made him contemplate the synthesis of Western medicine with ayurveda, the traditional Indian system of medicine.

Opting for a close study of Western research techniques, he sailed for the USA in 1923. After receiving his diploma from the Harvard School of Tropical Medicine, SubbaRow entered the Biochemistry Department of Harvard Medical School. Here he worked with Fiske, his

Figure 1 Informal portrait of SubbaRow by Philip Rane (circa 1948)

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supervisor, to develop the well-known Fiske–SubbaRow Method for determining the phosphorus content of tissues.[7] Fiske and SubbaRow went on to co-discover phosphocreatine in 1925[8] and ATP in 1929 (Fig. 1).[9]

SubbaRow then slowly came out of Fiske's laboratory to join the hunt for vitamins. Lederle Laboratories, which provided him secure supplies of liver concentrates for his vitamin hunt, persuaded SubbaRow to leave Harvard in 1940 to head its pharmaceutical research. At Lederle, SubbaRow led a team of biochemists to isolate folic acid from the liver in April 1943 and from fermentation broths of *Corynebacterium* sp. six months later as well as to synthesize it in August 1945. When the time came to put down the list of names on the publication,[10] SubbaRow chose to put his name alongside the team in alphabetical order (Fig. 2).

SubbaRow was drawn inexorably into anti-cancer research when the Lewisohn group at New York's Mount Sinai Hospital reported a series of inexplicable gross anomalies: (i) folic acid inhibited the growth of transplanted cancer cells in mice,[11] (ii) it caused a complete disappearance of breast cancer in 39 of the 89 mice treated,[12] (iii) teropterin, one of folic acids conjugates, caused complete regression of breast tumors in 40% of the mice,[13] and (iv) teropterin brought about a remarkable prolongation of life and considerable easing of pain in Babe Ruth, the baseball legend suffering from a tumor in the neck.[14] High hopes of a cancer cure were dashed when a sceptical SubbaRow established additional clinical trials, notably by Farber and his colleagues at Boston's Childrens Hospital, Peter Bent Brigham Hospital, and New England Deaconess Hospital. Teropterin was withdrawn from cancer therapy after these clinical studies showed it had at best an ameliorative effect.[15] The episode, however, served to draw attention to folic acid derivatives for a possible role in the chemotherapy of cancer.

Figure 2 J.H. Mowat, R.B. Angier, Y. SubbaRow, J. Semb, J.H. Boothe – five of 16 organic chemists who synthesized folic acid

One such derivative was x-methyl folic acid, which was a folic acid antagonist. SubbaRow used this compound in animal studies and conveyed verbally to Farber at Boston, even as the findings were being published in the *Journal of Biochemical Chemistry*: This preparation might be used experimentally in an attempt to modify blood dyscrasias marked by erythrocytosis or leukocytosis.[16]

Pteroylaspartic acid prepared by Hutchings and Mowat served as an even more impressive folic acid antagonist in SubbaRow's laboratory.[17] Aminopterin, more than 100 as powerful an antagonist as pteroylaspartic acid, was synthesized by Seeger of the collaborating Calco Laboratories in September 1947.[18] With aminopterin, Farber *et al.* secured remissions from acute leukemia in children and helped SubbaRow launch the chemotherapy of cancer.[19]

Experiments under the continued guidance of SubbaRow indicated that aminopterin toxicity could be modified by manipulating its molecule. Replacement of glutamic acid by aspartic acid raised the lethal dose, and methylation or hooking the methyl ($-CH_3$) radical to either the carbon atom at position 9 or the nitrogen atom at position 10 reduced the toxicity. The latter compound is amethopterin, which is better known as methotrexate, which too was synthesized by Seeger.[20, 21] Methotrexate is about one-fifth as toxic as aminopterin but requires five times the dose for equivalent action, so much so the ill effects from the two are the same at comparable dosage levels. It, however, allows physicians to adjust the dosage to get the best out of the treatment for the patient and has become a drug of choice in many cancers.

In psoriasis, Richard Gubner of the State University of New York College of Medicine teamed up with physicians for the clinical trial at Kings County Hospital of aminopterin in psoriasis because a series of papers presented on aminopterin success in leukemia by SubbaRow's research team to the New York Academy of Sciences on July 21, 1948, and 1950 and a connected paper published by a collaborative group at the John Hopkins University School of Medicine in 1949 showed that it was a potent inhibitor of connective tissue proliferation.

Gubner first established a collaborative study with Oleson, the associate of SubbaRow. The Oleson–Gubner study established that aminopterin suppressed inflammation and ameliorated symptoms of formalin arthritis in rats. Gubner ventured therefore to treat rheumatoid arthritis with aminopterin and stumbled into a breakthrough in the treatment of psoriasis.[2–4] L.R. was among Gubner's first group of seven patients with arthritis and one suffering from acute rheumatic fever at Kings County Hospital. L.R.'s arthritis began to improve on the third

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day of aminopterin and gradually improved, until at the end of the second week he was able to walk normally for the first time since the onset of his illness. Noticeably, psoriatic scaling also ceased after a week of aminopterin, and over the following week there was a striking improvement, and the skin became normal in appearance. Encouraged by the new therapy, the Gubner associates administered aminopterin to six chronic psoriatic patients and secured equally striking remissions: scaling ceased within two weeks, and lesions cleared markedly over the ensuing week. The lesions reappeared in 3–8 weeks but disappeared on resumption of aminopterin.

Aminopterin therapy could not be continued for long because of mucosal ulceration and other side effects. Remission and toxic changes occurring at the same time, there was no margin between therapeutic and toxic dosage. This imposed serious limitations on clinical use of aminopterin. The toxicity was overcome with citrovorum factor, which however neutralized the drug's therapeutic effects. These reports attracted widespread attention among dermatologists. Rees *et al.* used conservative dosages of aminopterin, and cleared or improved psoriasis without too high an incidence of toxic effects.[22] At the 75th Annual Meeting of the American Dermatological Association at Bellaire, FL, USA, on April 18, 1955, the three physicians presented a paper saying aminopterin is a potentially dangerous drug. Although it could favorably influence psoriasis, the range between beneficial and toxic doses was narrow. In the discussion that followed the presentation, Norman N. Epstein, their mentor, said aminopterin should be given only to those cases with severe generalized psoriasis.

With these ambivalent reports, aminopterin in psoriasis might have found a footnote in medical history. But, as it happened with leukemia, psoriasis became treatable though not curable with antifolics because of the switch from aminopterin to methotrexate made by the dermatologist duo, Edmundson and Guy, of Pittsburgh. Their interest in SubbaRow's aminopterin was first aroused by Gubner affecting clinical improvement of psoriasis with it in Brooklyn and the accompanying reduction in hyperkeratosis observed by Rees in San Francisco.

Despite the prudence called for in its use because of the drug's toxicity, the Pittsburgh pair were lured by antifolics when Rhoads at Memorial Hospital and Sloan-Kettering reported about the preferential use of methotrexate, the answer of SubbaRow to toxicity of aminopterin in the chemotherapy of cancer.[23, 24]

The Pittsburgh pair's 62 psoriatics were treated with either aminopterin (32) or methotrexate (17) or with both, one after the other (13). Good to excellent results were obtained in 24 of the 32 treated with aminopterin. Only four of the 17 treated with methotrexate did not respond satisfactorily. The 13 treated with aminopterin first and methotrexate next had remissions with equal rapidity for the same durations. Of the 29 who received only one drug (either aminopterin or methotrexate), 23 responded well or excellently.

As in leukemia, the effective daily dosage in psoriasis was five times (2.5 mg) with methotrexate compared with aminopterin (0.5 mg). No serious untoward reactions were encountered probably due to their limitation of dosage and rest periods between each course.[5]

In the decade following the publication of the Pittsburgh pair's clinical trials with folic acid antagonists, methotrexate was widely used in the treatment of psoriasis in preference to aminopterin. In 1972, the US Food and Drug Administration approved methotrexate therapy for psoriasis after the first guidelines were published in 1988.[25]

Methotrexate by itself or in combination with other drugs remains a valuable and inexpensive therapeutic option for patients and is widely used primarily in psoriasis but also in psoriatic arthritis as well as sarcoidosis, dermatomyositis, and pyoderma gangrenosum as Kalb *et al.* have noted in their review presented at the National Psoriasis Foundation Consensus Conference.[26]

The FDA approval of biologicals – alefacept, efalizumab, infliximab and adalimumab – brought about another dramatic change in the treatment of psoriasis, but their costs are prohibitive, and safety profile is still under study. Hence, methotrexate remains the preferred therapeutic option for psoriatics.

Several articles have been published regarding SubbaRow and his work in the world of medicine.[27–30] There are websites devoted to his life and work as well: http://www.ysubbarow.info/Archive/home.php and http://www.ysubbarow.info/

Over the eight years from 1940 to 1948, SubbaRow brought out folic acid, antifolics, aureomycin and diethylcar-

Figure 3 SubbaRow Library in Pearl River, NY, USA

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bamazine.[6] Little, however, is known about him, a wizard of wonder drugs, because of his reluctance to step into the limelight. SubbaRow was a poor businessman is the answer of a patent attorney who, after going through his laboratory records, was convinced of his genius as a chemist and was astonished he had not taken any of the steps that scientists everywhere consider routine for linking their name to their handiwork.

He was invariably in the audience when a colleague or a collaborator, pushed by him to the limelight, took the bow as each fruit of research directed by SubbaRow was revealed to the public (Fig. 3). He never granted interviews to the press. He never made the rounds of the academies that apportion accolades among the achievers. He never went on lecture tours. He never did any of these and other things required of anyone with the least pretension to awards, honours, and recognition. SubbaRow never presented himself as a candidate for any honour. Leading teams of young scientists and amateur experts to present the medical world with miracle cures, he chose to say: The victories of science are rarely won single handed. No one man should get the credit.

SubbaRow's last expressed wish to colleagues was that if God would spare him another couple of years, maybe he could cure another disease. Methotrexate must be hailed as a posthumous realization of this wish of Yellapragada SubbaRow (Fig. 4). Well, we now know that there are no cures for metabolic diseases that can at best only be ameliorated or managed. As the buzz word goes, psoriasis has, like many a metabolic disease, become treatable if not curable.

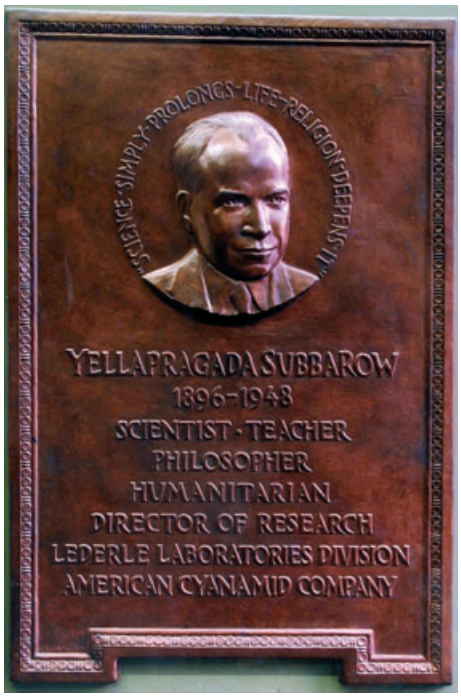

Figure 4 Memorial plaque at Lederle Laboratories

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